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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/581,140	05/30/2007	Joseph D. Buxbaum	7703/9	1982

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EXAMINER	
BAUSCH, SARAE L	
ART UNIT	PAPER NUMBER
1634	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/581,140	BUXBAUM ET AL.	
	Examiner	Art Unit	
	SARAE BAUSCH	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Currently, claims 1-3 are pending in the instant application. Claim 4-23 have been canceled. Claims 1 has been amended. This action is written in response to applicant's correspondence submitted 11/09/2010. All the amendments and arguments have been thoroughly reviewed but were found insufficient to place the instantly examined claims in condition for allowance. The following rejections are reiterated from the previous office action. Any rejections not reiterated in this action have been withdrawn as necessitated by applicant's amendments to the claims. Specifically the rejections under 35 USC 112, 2nd paragraph have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is Final**.

Maintained Rejection

Claim Rejections - 35 USC § 112- Enablement

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims

The claims are drawn to method for identifying relative genetic risk for autism in an individual comprising determining the genotype at polymorphism sites rs2056202 and/or rs2292813.

The claims encompass analysis of relative genetic risk for autism and identifying polymorphisms at sites rs2056202 and rs2292813 in any individual, human or non-human.

The nature of the invention, therefore, requires the knowledge of a robust and reliable correlation between association between the polymorphisms rs2056202 and rs2292813 and susceptibility to autism.

Guidance in the Specification and Working Examples

The specification asserts an association between increased risk of autism in individuals having a G allele at either or both polymorphism sites rs2056202 and rs2292813 of SLC25A12 gene. The specification asserts identifying rs2056202 and rs2292813 and genotyping 411

autistic families, including linkage and association tests carried out in 197 informative families. The specification asserts that linkage and association between autistic disorder and rs2056202 and rs2292813 was observed (see pg. 9, example 1). The specification asserts that the evidence for association of rs2056202 and rs2292813 in a small number of cases and controls was determined (See pg. 13). Table 1 demonstrates that rs2292813 was not associated with paternal transmission nor was the haplotype G*A associated in table 1 or table 2. The specification teaches that with all association studies especially complex disorders thought to be due to multiple interacting genes of weak effect such as autism, replication in independent samples must be completed before the results can be accepted. The specification teaches that the study presented lacks power, where many of the parents were homozygous at the two loci and a carefully designed case-control study with control matched for ethnicity, gender and age may have more power to detect association at these two loci or alternatively genotyping several hundred trios for TDT would be in order for a replication study (See pg. 18 last paragraph cont'd to page 19). Furthermore the specification teaches that the susceptibility variants are common alleles which would not be immediately useful for genetic counseling until it can be considered together with additional loci (see pg. 19, lines 8-14).

Thus the specification demonstrates the unpredictability of the association rs2056202 and rs2292813 with risk of autism and demonstrates the need for replication studies to validate the data presented in the specification. The specification demonstrates the unpredictability by teaching that susceptibility allele, G at position rs2056202 and rs2292813 is the common allele and would not be useful for genetic counseling until further studies are replicated, including carefully designed case-control studies and studies with more power.

The state of the prior art and the predictability or unpredictability of the art:

There is a large body of knowledge in the prior art related to polymorphisms in general, and their association with diseases or disease states. However, the art exemplifies the unpredictability with regard to the functionality of polymorphic sites in genomic DNA. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a disease state, a physiological state, or drug metabolism or response. The art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn et al. suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn et al. caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

Additionally, Ioannidis (Nature Genetics, Vol. 29, pages 306-309, November 2001) teaches that the results of the first study correlate only modestly with subsequent research on the same association (abstract). Ioannidis teaches that both bias and genuine population diversity might explain why early association studies tend to overestimate the disease protection or

predisposition conferred by a genetic polymorphism (abstract). Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the p-globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 1998; 281 (5384):1787-1789).

At the time the invention was made, the art was silent with regard the presence of a G allele at position rs2056202 and rs2292813 of SLC25A12 association with increased risk of autism. The specification teaches that replication studies are necessary to validate the association of rs205602 and rs2292813 and risk of autism, as the study presented in the instant application is under powered and since the susceptibility alleles are the common allele would not be immediately useful for genetic counseling (see pg 19). The post filing art teaches that in replication studies the G allele of rs2056202 and rs2292813 of the SLC25A12 gene was not associated with risk of autism. Chien (Progress in Neuro-Psychopharmacology and Biol Psych, 2010, vol 34, pp 189-192) teaches genotyping rs2056202 and rs2292813 of 465 patients with autism and 450 control subjects from Taiwan (see methods). Chien demonstrates that the SLC25A12 gene is not associated with autism in their population. Chien teaches that genetic associations are well known for their inconsistent results among different studies and teach that clinical heterogeneity of patients, including different research groups recruiting patient with different severity of symptoms and varied symptom dimensions, however their study included only autistic disorder. Chien teaches their study is the largest sample size in a genetic study of the SLC25A12 and autism in the literature and even this sample size has limited power and

teaches that larger sample size or meta-analysis is needed to address the association of SLC25A12 gene and autism (see pg. 193). Correia (J Autism Dev Disord 2006, 36:1137-1140) teaches testing the association of rs2056202 with autism (see pg. 1138). Correia demonstrate that rs2056202 in their population was not associated with autism and suggest that different physiological mechanism may be involved and teach that additional population will be required for a definite conclusion (see pg. 1139). Rabionet et al. (Am J Psychiatry, 2006, 163:929-931) demonstrates an independent study of 327 families with autistic offspring to test the association of SNPs rs2056202 and rs2292813. Rabionet teaches genotyping alleles and haplotypes including sites rs2056202 and rs2292813 of the SLC25A12 gene and concludes there is no evidence of an association between SLC25A12 and autism (see results). Rabionet teaches that no association was found for individual SNPs, haplotypes, or families with positive lod scores (see pg. 930). Rabionet teaches that population differences could account for the different results or the associated described by applicants own work could be caused not by a variation in SLC25A12 but a variation nearby gene or that association could be due to a type I error. Blasi (Eu. J. Human Gen. 2006, 14:123-126) demonstrates that SLC25A12 is not associated with autism in a multiplex family sample. Blasi demonstrates that SNPs rs2292813 and rs2056202 was not found to be associated with autism and not likely to contribute strongly to autism susceptibility (see pg. 125).

As exemplified by the post filing date art, a large amount of unpredictability exists regarding the association of SNPs at polymorphic position rs2056202 and rs2292813 in the SLC25A12 gene and autism. As taught in the specification, replication studies are needed to determine the validity of the association and as demonstrated by the post filing art (Chien,

Rabionet, Blasi) autism is complex disease and population differences may account for different association results, thus demonstrating the unpredictability of SNP association studies and specifically demonstrating the unpredictability of associating increased risk of autism with the presence of a G allele at either or both polymorphic positions, rs2056202 and rs2292813, of the SLC25A12 gene in any individual, human and non-human.

The level of skill in the art:

The level of skill in the art is deemed to be high.

The quantity of experimentation necessary:

To practice the invention as broadly as it is claimed, the skilled artisan would have to perform a replication study of a large study family based and population based study to predictably determine the association of either or both polymorphic sites rs2056202 and rs2292813 with a G allele and autism. The art confirms the need for such study, as well as teaching that the outcome of such study is unpredictable as several replication studies were unable to reproduce that the presence of a G allele at position rs2056202 or rs2292813 is associated with autism.. The assessment of polymorphisms with regard to phenotypes and disease states, particularly complex diseases such as autism is highly unpredictable. Given the polymorphic nature of genomic DNA as well as the fact that different populations of people possess different combinations of specific alleles, large population based studies are required to accurately assess the identity of any particular SNP in terms of association to disease state or

phenotype, especially in complex diseases such as autism. The experimentation required by the skilled artisan to make and use the instant invention, as broadly as it is claimed, would be replete with unpredictable trial and error analysis, with many intervening steps requiring a large amount of inventive effort. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the conflicting data provided in the specification, the lack of guidance in the prior art as well as the teachings and examples of unpredictability in the post filing date art, balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the methods of the claims as broadly written.

Response to Arguments

4. The response traverses the rejection on pages 3-4 of the response mailed 11/9/2010. The response asserts that the working examples demonstrate that the presence of a G at either rs2056202 or rs2292813 of SLC25A12 gene is indicative that a human may be at risk for autism and points to examples 1 and 2. As stated in the rejection above, the specification asserts that linkage and association between autistic disorder and rs2056202 and rs2292813 was observed (see pg. 9, example 1). The specification asserts that the evidence for association of rs2056202 and rs2292813 in a small number of cases and controls was determined (See pg. 13). Table 1 demonstrates that rs2292813 was not associated with paternal transmission nor was the haplotype G*A associated in table 1 or table 2. The specification teaches that with all association studies especially complex disorders thought to be due to multiple interacting genes of weak effect such as autism, replication in independent samples must be completed before the

results can be accepted. The specification teaches that the study presented lacks power, where many of the parents were homozygous at the two loci and a carefully designed case-control study with control matched for ethnicity, gender and age may have more power to detect association at these two loci or alternatively genotyping several hundred trios for TDT would be in order for a replication study (See pg. 18 last paragraph cont'd to page 19). Furthermore the specification teaches that the susceptibility variants are common alleles which would not be immediately useful for genetic counseling until it can be considered together with additional loci (see pg. 19, lines 8-14). Thus the specification demonstrates the unpredictability of associating G allele or rs2056202 and rs2292813 with autism.

The response asserts that Chien teaches that the association of rs2056202 and rs2292812 of the SLC25A12 gene with autism has been replicated in an Irish sample (Serguando 2005) and Finnish sample (Turunen, 2008) and teaches that rs2056202 was associated with routine and ritual behaviors in autism (Silverman 2008). The response asserts that Chien concluded that these studies support that SLC25A12 gene is a risk gene for autism. The response asserts that although Chien did not find an association in its sample of Han Chinese from Taiwan Chien states that heterogeneity of genetic etiology of autism in different populations may account for differences seen in various studies. The response further asserts that Rabionet suggest that population differences could account for different results. This response has been thoroughly reviewed but not found persuasive.

Although Chien and Rabionet teach that differences in population could account for different results neither the specification nor the art teach which population will be predictably associated with risk of autism. The specification nor the art provide guidance to predictably

determine which population will be associated with autism by detecting the common G allele of rs2056202 or rs2292812. Furthermore the specification teaches that larger replication studies are needed to confirm the association, thus based on the teaching in the specification coupled with the post filing art that teaches the unpredictability of different populations accounting for different risk association, the amount of experimentation that would be necessary to make and use the instant invention, as broadly as it is claimed, would be replete with unpredictable trial and error analysis, with many intervening steps requiring a large amount of inventive effort. Additionally, Turunen, cited by applicant, teaches that negative reports exist and therefore it is important to perform combined data analyses or to employ meta-analysis methodology to further determine the significant of SLC25A12 variants across different samples as well as to analyze yet additional autism samples to elucidate potential role of SLC25A12 (see pg. 191, 2nd para). Turunen teaches that extensive studies are needed to confirm the role of SLC25A12 to identify the actual predispositioning allelic variant (See pg. 191, last para). Thus Turunen further demonstrates the unpredictability for identifying rs2056202 or rs2292812 with a predictably association of increased risk of autism. Thus although two studies, Silverman and Serguando found an association with autism, several studies, including Turune, Chien, Rabionet, Blasi, Correia all demonstrate the need for further evaluation thus demonstrating the unpredictability of associating rs2056202 or rs2292812 with autism. Therefore, based on the teaching in the specification that replication studies are needed to determine the validity of the association, coupled with the preponderance of evidence in the art that associating rs2056202 or rs2292812 with autism is not correlative, the large quantity of research required to define these unpredictable variables, the conflicting data provided in the specification, the lack of guidance in

the prior art as well as the teachings and examples of unpredictability in the post filing date art, it would require undue experimentation for one of skill in the art to perform the methods of the claims as broadly written.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Conclusion

5. No claims are allowable.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARAE BAUSCH whose telephone number is (571)272-2912. The examiner can normally be reached on M-F 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Sarae Bausch /
Primary Examiner, Art Unit 1634